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10/520,360

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Julie Kay Bush

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EXAMINER

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/520,360
Filing Date: January 05, 2005
Appellant(s): BUSH ET AL.

John A. Cleveland, Jr., Ph.D.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 9/22/2008 appealing from the Office action mailed 4/30/2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct

(4) Status of Amendments after Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

Withdrawn Rejections

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The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner after the appeal conference: 1) 35 USC § 102(b) over TEICHER et al and 2) 35 USC § 35 102(e) over HEATH.

Maintained Rejections

Claims 2 and 15 are rejected under 35 USC § 103(a) as being obvious over TEICHER et al. and HEATH et al. are to be reviewed on appeal.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

US 5,545,636	HEATH, Jr. et. al.	8-1996
WO02/02094	TEICHER, B. et al.	10-2002

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

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Claims 2 and 15 are rejected under 35 USC § 103(a) as being obvious over TEICHER et al¹.

TEICHER et al discloses 3-[1- (1-(pyridin-2 methyl)piperidin-4-yl)-indol-3-yl]-4-(1 -methylnol-3-yl)- 1H-pyrrole-2,5-dione (FB) or a pharmaceutically acceptable salt or solvate thereof (see lines 1-10 on page 7). It further teaches, “Because it contains a basic moiety, the compound of Formula I can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as **hydrochloric acid** (lines 13-32, page 8). Reference further teaches that the pharmaceutically acceptable salts of the compound of Formula I can also exist as **various solvates, such as with water**, methanol, ethanol, dimethylformamide, ethyl acetate and the like. **Mixtures of such solvates can also be prepared**. The source of such solvate can be from the **solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent**. See lines 29-32, page 8. The reference further teaches that particularly hydrochloride and mesylate salts are used, see line 27 and 28, page 8).

Instant claims differ from the reference in claiming crystalline monohydrochloride of FB wherein the prior art teaches dihydrochloride salt (see lines 27-31 on page 11) of the same compound. TEICHER et al teaches the present compound, FB, and its hydrochloride salts especially crystalline dihydrochloride salts. The reference teaches the compound, compositions, and methods of treating neoplasm, and the combination with other antineoplastic agents.

It would have been obvious to one skilled in the art at the time of invention to prepare the crystalline pharmaceutically acceptable salts such as hydrochloride salts because the prior art

¹ BEVERLY TEICHER et al; World Intellectual Property Organization Publication Number WO 02/02094 A2,

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TEICHER et al teaches the crystalline forms of dihydrochloride and teaches that since it contains a basic moiety, it can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric acid (lines 13-32, page 8), so the monochloride salt would be fairly suggested thereby.

35 USC § 103(a) --- Second Rejection

Claims 2 and 15 are rejected under 35 U.S.C. 103(a) as being obvious over HEATH et al.

HEATH et al discloses 3-[1- (1-(pyridin-2 methyl)piperidin-4-yl)-indol-3-yl]-4-(1 -methylnol-3-yl)- 1H-pyrrole-2,5-dione (FB). See example 49 in column 45 where the compound is disclosed. This compound is a protein kinase inhibitor. The reference teaches pharmaceutically acceptable salts such as hydrochloric salts.² See the entire document especially lines 37-67 in column 10; lines 1-12 in column 11. The reference also teaches the compounds are potent, beta-1 and beta-2 isozyme selective PKC inhibitors.

In claims 2 the Appellants have cited the X-ray diffractions of their crystalline compound. However, since the compound are potent, beta-1 and beta-2 isozyme selective PKC inhibitors, one skilled in the art at the time of invention would have been motivated to prepare the crystalline acid addition salts pharmaceutically acceptable salts such as hydrochloride salts because HEATH et al teaches the crystalline forms of this compound. The pharmaceutical composition will be the same as the prior art because the compound is the same as presented.

published January 10, 2002. See the entire document, especially lines 6-10 on page 9, lines 1-10 on page 7, lines 27-30 on page 11, all of pages 12-20, examples, 49 and claims.

⁵ WILLIAM F. HEATH, JR. et al; United States Patent No. 5,545,636, published August 13 1996. See the entire document especially example 49 in columns 45 and 46, formulas II and III in column 3 and 4, lines 37-67 in col. 10; lines 1-4 in column 11.

(10) Response to Argument

35 USC § 103(a) --- First Rejection

Appellant argues that the TEICHER does not teach the crystalline monohydrochloride of 3-[1- (1-(pyridin-2 methyl) piperidin-4-yl)-indol-3-yl]-4-(1 -methyhndol-3-yl)- 1H-pyrrole-2,5-dione (FB) as has been presently claimed in claim 2. Examiner respectfully disagrees because TEICHER et al teaches the dihydrochloride of FB in example 49. It teaches the same compound 3-[1- (1-(pyridin-2 methyl) piperidin-4-yl)-indol-3-yl]-4-(1 -methyhndol-3-yl)- 1H-pyrrole-2,5-dione (FB) or a pharmaceutically acceptable salt or solvate thereof (see lines 1-10 on page 7). It further teaches, "Because it contains a basic moiety, the compound of Formula I can also exist as pharmaceutically acceptable **acid addition salts**. Acids commonly employed to form such salts include inorganic acids such as **hydrochloric acid** (lines 13-32, page 8). The reference further teaches that the pharmaceutically acceptable salts of the compound of Formula I can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the **solvent of preparation or crystallization**, or **adventitious** to such solvent (lines 1-5, page 9). Therefore, Examiner believes that TEICHER et al teaches the present compound, FB, and its crystalline salts, especially crystalline **dihydrochloride salts** and provides motivation to prepare any hydrochlorides salts. No distinction has been made from prior art crystallized dihydrochloride compound and X-ray diffraction of Appellants monohydrochloride compound. The peaks as presented in claim 2 are

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not sufficient to overcome the rejection. This dihydrochloride of FB compound has been exemplified by the prior art.

Additionally "comprising" allows other peaks to be added. Therefore, the X-ray diffraction peaks presented in claim 2 are not sufficient and is not limited to monohydrochloride. The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps, comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts".

Appellant further argues that relies in six sections of the reference. Examiner respectfully disagrees because claims are not drawn to method of using these compounds. Claims 2 and 15 are drawn to crystalline monohydrochloride of FB and its composition.

Appellants argue that courts have been consistent in stating that polymorphs are patentable subject matter. Examiner believes that Appellant have not established that the compound is a different polymorph. *In re Cofer* has been cited but is not considered proper in this case because the hydrochloride of FB is taught by the prior art. Here Appellant in their own specification lines 8-18 on page 2 discloses that the dihydrochloride of FB is crystalline. Here the compounds are in the form of hydrochloride salt. Citation of *In re Jones* is not applicable in this case because claims 2 and 15 are not generic and prior art does teach crystalline dihydrochloride of FB. In present case prior crystallized forms of FB dihydrochloride. Appellants in the specification disclose that dihydrochloride of FB exists in crystalline form. See lines 12-18 on page 2.

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Since this compound of the prior art is the closest prior art Appellants should compare the data of the prior art compound (dihydrochloride and their claimed monohydrochloride).

Appellants cited Pfizer v. Apotex Pfizer v. Apotex, 82 USPQ2d 1321, 1336, 1338 (Fed. Cir. 2007). This decision supports Examiner's position that the formation of a new salt was considered obvious. It states that "optimization of the acid addition salt formulation for an active pharmaceutical ingredient is obvious where the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art suggests the particular anion used to form the salt. Moreover, one skilled in the art would expect various anions to provide salts having a range of properties, some of which would be superior, and some of which would be inferior, to any given salt". In present case preparation of crystalline monohydrochloride salt v. crystalline dihydrochloride salt is considered obvious because there is no evidence or comparison between the prior art teaches crystalline dihydrochloride and presently claimed crystalline monohydrochloride.

35 USC § 103(a) --- Second Rejection

Appellant argues that HEATH et al does not teach the monohydrochloride salt of FB. Examiner respectfully disagrees because the reference teaches the FB, its pharmaceutically acceptable salts such as hydrochloric salts. (example 49 in column 45). It further teaches that the pharmaceutically acceptable salts of the compound of Formula I can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. The source of such solvate can be from the solvent of crystallization, inherent in the **solvent of**

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preparation or crystallization, or adventitious to such solvent. In claims 2 the Appellants have cited the X-ray diffractions of their crystalline compound. However, since the compound are potent, beta-1 and beta-2 isozyme selective PKC inhibitors, one skilled in the art at the time of invention would have been motivated to prepare the crystalline acid addition salts pharmaceutically acceptable salts such as hydrochloride salts because HEATH et al teaches hydrochlorides of this compound. The pharmaceutical composition and the method of using will be the same as the prior art because the compound is the same. No distinction has been made by the Appellants.

Appellants have provided no data or evidence for distinguishing their invention with the prior art. Due to the teachings of the prior art presently claimed invention is considered prima facie obvious to one skilled in the art because prior art teaches the base compound FB and teaches crystalline acid addition salts pharmaceutically acceptable salts such as hydrochloride salts. Appellants provide no evidence to establish why their compound should be considered non-obvious, in absence of additional evidence to contrary, Appellants' evidence must be deemed insufficient.

Appellants cite *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966) which is not considered proper in this case because the hydrochloride of FB is taught by the prior art. Here Appellant in their own specification lines 8-18 on page 2 discloses that the dihydrochloride of FB is crystalline. Here the compounds are in the form of hydrochloride salt. (Claims to the free-flowing crystalline form of a compound were held unobvious over references disclosing the viscous liquid form of the same compound because the prior art of record did not suggest the claimed compound in crystalline form or how to obtain such crystals.). Appellant argue that

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prior does not teach specific crystalline form with specific XRD pattern. Claim 2 may contain mixtures of monohydrochlorides and dihydrochlorides or any other compounds because “comprising” does not limit the peaks specific to their claimed monohydrochloride. When the compounds are known in crystalline hydrochlorides form, it would have been obvious to one skilled in the art to prepare any hydrochloride salt at the time the invention was filed.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner’s answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Sabiha Qazi/

Sabiha N. Qazi, Ph.D.

Primary Examiner Art Unit 1612

Conferees:

/Frederick Krass/

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